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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/068,507	07/15/98	EIJSINK V	1380-122PCT

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1652	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary

Application No.	Applicant(s)
09/068,507	Eijsink et al.
Examiner	**Group Art Unit**
Elizabeth Slobodyansky	1652

☒ Responsive to communication(s) filed on *Oct 16, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *44-66* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *44-66* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

The request filed on October 16, 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/068,507 is acceptable and a CPA has been established. An action on the CPA follows.

The preliminary amendment filed October 16, 2000 canceling claim 16-43 and adding claims 44-66 has been entered.

As part of the preliminary amendment filed October 16, 2000, Applicants submitted a letter from Blackwell Science Ltd., which publishes the journal *Molecular Microbiology*, confirming that *Molecular Microbiology* (1995) 18: 631-639 containing the Diep et al. paper was published on 13 December 1995. This letter disqualifies the Diep et al. (1995) paper as a prior art.

Claims 44-66 are pending.

Specification

The specification is objected to because the headings of the parts of the description are missing.

Claim Objections

Claims 44 and 45 are objected to because "and" between "(c)" and "(d)" is missing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 44-65 encompass "a first inducible promoter" or "a promoter" that is induced by the expression product of the SakR gene.

The specification discloses that "the expression of genes under control of the promoter element depicted in Fig.4 is dependent on the expression of IF-K-R gene cluster (Fig.1) (page 7, lines 19-21). However, the detailed mechanism of such activation is not described. The specification discloses the expression product of the IF gene that activates the chain of reactions resulting in the production of sakacin P. The specification does not teach the induction of any promoter by the SakR gene expression product per se. The examiner is unable to locate adequate support in the specification for such claim.

Furthermore, Applicants submit that "SakK and SakR are not considered inducing agents" (remarks, page 9, penultimate paragraph). There is no indication that a promoter directly inducible by the SakR gene expression product was within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claim 44-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 44 and claims dependent therefrom encompass a genus of a first inducible promoter, an IF gene, a SakK gene, a SakR gene, the expression products of said genes and functional analogs thereof.

Applicants teach that "[i]n the present invention references to the group IF, K and R (or analogs thereof) should be interpreted as a reference to IF, K, R and such a possible extra gene if it would appear to exist" (page 21, lines 17-20 and the sentence bridging pages 10 and 11, emphasis added). Therefore, the claims encompass

elements not only not sufficiently described but also not yet discovered at the time the application was filed.

Applicants disclose IF gene, SakK gene, SakR gene and the promoter of the IF gene of the sakacin P producing *Lactobacillus sake* LTH673. Therefore, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. No common structural attributes identify the members of the genus. Given this lack of description of common structural attributes or characteristics that identify members of the genus of an IF gene, a SakK gene or a SakR gene having the requisite properties, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 44-65 recite "a first inducible promoter" or "a promoter" that is induced by the expression product of the SakR gene.

The specification discloses that "the expression of genes under control of the promoter element depicted in Fig.4 is dependent on the expression of IF-K-R gene cluster (Fig.1) (page 7, lines 19-21). However, the detailed mechanism of such activation is not described. The specification does not teach the induction of a promoter by the SakR gene expression product. The specification discloses the expression product of the IF gene that activates the chain of reactions resulting in the production of

sakacin P. This inducer has the amino acid sequence corresponding to residues 19-37 of SEQ ID NO:3 and unlike sakacin P does not exhibit anti-microbial activity. Thus, the representative number of species is one.

Applicants describe the expression product of an IF gene as "not a lantibiotic". Therefore, any other polypeptide including the one exhibiting anti-microbial activity and encoded by the same gene as a bacteriocin is encompassed by the claims. Structural features and other properties that could distinguish said IF expression product from the prior art are missing from the disclosure. No common structural attributes identify the members of the genus.

The prior art does not teach and does not allow to predict other members of an IF gene expression product that is not a lantibiotic and is able to induce the production of a bacteriocin. As admitted by Applicants in their Remarks filed October 16, 2000 prior to the instant invention "nothing was known about inducing compounds related to bacteriocin production" (page 17, final paragraph). However, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. No common structural attributes identify the members of the genus. Given this lack of description of common structural attributes or characteristics that identify members of the genus of an IF gene expression product having the requisite properties, the specification fails to sufficiently describe the claimed invention in such full, clear,

concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim 52 recites a plnC gene or a plnD gene as a functional analogue of SakR gene. The specification does not teach the common attributes of these genes. It is not disclosed whether plnC gene and a plnD gene both have the same function as the SakR gene. Claim 52 recites plnA as a functional analogue of the IF gene and plnB as a functional analogue of the SakK gene.

However, the same gene, plnA, encodes a bacteriocin In the plantaricin system Therefore, it appears that the plantaricin system is more similar to the nisin system than to the sakacin P system. The expression product of an IF gene, an inducer, and sakacin P, a bacteriocin, are encoded by different genes. Applicants fail to point out the features of a bacteriocin cluster that impart the ability to produce both an inducing agent and a bacteriocin wherein they are not the same.

There is also no teaching in the specification as to what are the common distinguishing features shared by the members of the genus of an IF promoter inducible by the expression product of an IF gene that would distinguish it from other promoters inducible by the expression products of their respective genes in bacteriocins' clusters. Thus, the representative number of species is one.

Claim 65 is drawn to an isolated nucleic acid comprising undefined number of nucleotides characterized by their location "30 to 38 nucleotides downstream from a -

10 region of a bacterial gene said sequence promotes transcription of an operatively linked coding nucleic acid sequence which is activated by an expression product of a SakR gene or functional analog thereof that has been activated by an expression product of SakK gene or functional analog thereof". This claim is drawn to extremely broad genus that is not described by either structure or clear function. The specification teaches the autoinduced system of the IF-K-R gene cluster is autoinduced by the secreted peptide encoded by IF (page 7, lines 23-24, for example). Therefore, the representative number of species is one.

Therefore, based on the instant disclosure, taken into account that the representative number of the disclosed species equals one and considering the state of the relevant art, it is unpredictable whether a nucleotide sequence will be induced by the IF gene expression product. Thus, a promoter inducible by the expression product of an IF gene lacks sufficient written description needed to practice the invention of claims 44-65.

Claim 44, with dependent claims 46, 48-62, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a gene expression system comprising a promoter inducible by the IF gene expression product, an IF gene, a SakK gene and a SakR gene, a kit comprising it and a method of use thereof, does not reasonably provide enablement for an expression system comprising

functional analogs of said elements and a kit and a method of use thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

The claims encompass engineered promoters and inducing agents of unknown structure. The following rejection is made over a first inducible promoter of an unknown structure inducible by a SakR gene expresiion product or by a functional analogue of an IF gene expression product of an unknown structure.

The specification teaches one IF gene product that induces its promoter. A functional analogue of a gene product can be a compound of various chemical classes and not necessarily peptides. It is impossible to make a compound without knowing its structure. Consequently, it is impossible to make a promoter that is inducible by unknown compound. The specification lacks guidance as to what are other compounds in addition to amino acid residues 19-37 of SEQ ID NO:3 that can induce the IF gene promoter. Moreover, as mentioned above, an analogue can be any molecule. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

Claim 65 is drawn to a part of any bacterial gene comprising an isolated nucleic acid comprising the undefined number of nucleotides characterized by their location "30 to 38 nucleotides downstream from a -10 region of a bacterial gene". The function of said sequence is to promote "transcription of an operatively linked coding nucleic acid sequence which is activated by an expression product of a SakR gene or functional analog thereof that has been activated by an expression product of SakK gene or functional analog thereof". This claim is so broad as to encompass any structure by function. However, the specification does not teach what are the structural requirements for the sequence to impart the requisite function. The state of the art does not allow the predictability of function based on structure.

Therefore, one of ordinary skill would require guidance, such as information regarding the structural limitations on a promoter and a functional analogue of its gene expression product, in order to make a first inducible promoter inducible by a SakR gene product or a functional analogue of an IF gene, SakK gene and SakR gene as well as analogues of said compounds in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 44-63 are confusing because they recite the mechanism of action of the expression system and do not distinctly claim the elements included therein. For example, it is unclear what compound induces the expression. difference between two sets of genes. For the same reasons claim 64 reads on a vector comprising a SakR gene and a host cell comprising the same gene.

Claim 65 is unclear as reciting "-10 region" of a bacterial gene. This can mean many regions.

Further, the expression product of an IF gene is defined as not a lantibiotic. Such limitation claims the invention by excluding what the inventors did not invent rather than distinctly and particularly pointing out what they did invent (MPEP 2173.05(i)).

Claim 46 is confusing as reciting a functional analogue of the expression product of an IF gene comprising residues 19-37 of SEQ ID NO: 3 whereas residues 19-37 of SEQ ID NO: 3 represent the native product.

The claims recite functional analogues. There is no art-accepted definition of said term.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 44-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Diep et al. (1994).

Diep et al. (1994, form PTO-1449) teach that the genes of plnABCD cluster in *Lactobacillus plantarum* C11 are transcribed from a common promoter inducible by

plantaricin (abstract). They cloned the entire unit that includes the regulatable promoter and comprises (page 161, 2nd column).

In their Remarks filed October 16, 2000 Applicants argue that "the true promoter, as disclosed in the present invention, is located down stream of the promoters annotated Diep et al (1994)" (Remarks, page 20, 1st paragraph). Applicants assert that Diep et al. disclose no promoter (Remarks, page 24, 1st paragraph). These arguments are not persuasive in relation to the invention as claimed. Diep et al. teach the sequence comprising said promoter and a later found function does not make said sequence novel.

Claims 44-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Tichaczek et al.

Tichaczek et al. (1994, form PTO-1449) teach the expression of sakacin P in LTH673. They teach a sequence comprising a promoter inducible by its gene expression product (abstract; page 362, "Methods"; page 363, Figure 2). The inducibility is an inherent characteristic of said promoter. The disclosed sequence comprises residues 7-14 and 30-38 of SEQ ID NO:6.

Claims 44-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Axelsson et al.

Axelsson et al. (form PTO-1449) teach the expression of sakacin A in *Lactobacillus sake* Lb706. They teach a sequence comprising a promoter inducible by its gene expression product (abstract; pages 2126-2127).

Claims 44-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Venema et al. (1994).

Venema et al. (1994, form PTO-1449) teach that the genes of pedABCD cluster of *Pediococcus acidilactici* that produces pediocin are transcribed from a common promoter (abstract). They cloned the entire unit that includes the regulatable promoter (page 516, Figure 1).

Claims 44-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Balaban et al.

Balaban et al. (form PTO-1449) teach that the production of exoproteins in *Staphylococcus aureus* is controlled by a global regulatory system, *agr* (abstract). They show that this system is autoinducible (abstract). The disclosed DNA comprises residues 6-7, 9-17 and 32-36 of SEQ ID NO:11 and residues 6-7, 9-17 and 32-36 of SEQ ID :12. *Staphylococcus* is the lactic acid bacterium.

Response to Arguments

With regard to Applicant's arguments filed October 16, 2000, it is noted that the description and enablement requirements must be satisfied at the time of filing while Applicants recite documents published at a later date.

Applicant's arguments do not clearly point out the patentable novelty which they think the claims present in view of the state of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

December 28, 2000